REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 1, 30, 41, 42, and 44 have been amended. Claims 45-46 are new. After entry of the amendment, claims 1, 3-21, and 30-46 will be pending. Claims 7-10 and 15-18 have been withdrawn from consideration by the Examiner.

Applicants submit the amendment is supported throughout the specification, including for example at page 23, lines 37-40, page 24, lines 11-16, and page 25, lines 8-15 and 24-33, and does not raise any issues of new matter.

Written Description

Claim 31 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action alleges the specification only teaches that the conditions recited in claim 31 are associated with edema in general and not with central nervous system (CNS) edema. Applicants respectfully do not agree.

The written description requirement must be applied in the context of the particular invention and state of the knowledge. *Capon v. Eschar*, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). It is unnecessary to spell out every detail of the invention in the specification. Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Falkner v. Inglis*, No. 05-1234, slip. op. at 14 (Fed Cir. May 26, 2006) (citing *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 Fed. Cir. 2005).

Applicants submit that one of ordinary skill in the art reading the application as a whole would understand that the inventor was in possession of the subject matter of claim 31. As an initial matter, applicants note that claim 31 is supported in the least at page 24, lines 11-17. This paragraph is located between a discussion of central nervous system and cerebral edema and further discussion of cerebral edema. When this paragraph is read in context, Applicants submit one of skill in the art would understand that these conditions would be applicable to CNS edema including cerebral edema. In addition, many of the conditions in the list are identified as relating

to CNS or cerebral edema such as trauma (such as head injury), cerebral malaria, encephalopathy, encephalitis, meningitis, and birth asphyxia.

Moreover, many of the conditions recited in claim 31 and disclosed at page 26 of the specification were known to be associated with CNS edema See, for example, the following enclosed abstracts:

- Feigin and Budzilovich, 1978, *J. Neuropathol. Exp. Neurol.*, 37:326-357 (cerebral edema demonstrated in metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy, disorders of amino acid metabolism, trauma, hypertensive disease, radiation effect, diffuse hypoxia with acidosis, and other conditions, both in disorders of myelin metabolism and in conditions in which normal myelin metabolism is injured by extrinsic influences);
- Batzdorf, 1976, *Pediatrics*, 58:78-87 (cerebral edema adds significantly to the morbidity from such diverse conditions as neonatal hypoxia and hypernatremia, water intoxication, meningitis, encephalitis, birth trauma, lead poison, and radiation therapy, as well as brain tumors and abscesses);
- Tietjen et al., 1996, *Crit. Care Med.*, 24:311-322 (acute hypertension may result in cerebral edema);
- Takahashi et al., 1991, *Am. J. Physiol. Heart Circ. Physiol.*, 261:H825-H829 (cerebral edema during hyperammonemia is associated with glutamine accumulation in the brain, inhibition of brain glutamine accumulation prevented cerebral edema).

In view of Applicants' disclosure and the knowledge in the art, one of skill in the art would have recognized that CNS edema is associated with the conditions recited in claim 31. Withdrawal of the written description rejection is respectfully requested.

New Matter

Claims 41 and 44 were rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The examiner indicates that this is a new matter rejection. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, the claims have been amended to recite administering the hVEGF antagonist within about four days after detection of the presence of cerebral edema. The amendment is supported

in the specification, for example, at page 25, lines 24-27. Withdrawal of the rejection is respectfully requested.

Enablement

Claims 1, 6, 30, 31, and 36-44 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

The Office Action acknowledges the specification enables treatment of cerebral edema associated with brain tumor, stroke, or head injury. According to the Office Action, the basis for the rejection is that the specification fails to provide adequate guidance for use of the claimed hVEGF antagonists for treatment of patients that have edema and one of the non-neoplastic conditions recited in claim 31. See Office Action at page 6. Applicants respectfully do not agree.

Applicants contend that one of skill in the art reading this specification would be able to practice the claimed methods. There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Some experimentation may be allowed as long as it is routine.

As an initial matter, Applicants do not agree that claim 6 is not enabled. Applicants note that claim 14 was not rejected. As described in the specification, Applicants submit that the methods of the disclosure provide for treatment immediately upon detection of a symptom of a stroke or cerebral edema. See the specification, for example, at page 25, lines 24-27. In addition, the working example provides an in vivo model of cerebral edema and describes administration of a VEGF antagonist before the development of focal cortical ischemia, at the time of reperfusion, and at 1 and 2 days following surgery. The working example indicates that administration of a VEGF antagonist prior to development of a symptom and immediately after one or more symptoms develop was described and exemplified in the specification. One of skill in the art could readily use this model system to conduct any further experimentation, if necessary, to determine the timing of treatment. Such experimentation would be routine.

Applicants submit one of skill in the art reading the specification would understand how to practice the methods of claim 6.

Claim 31 is not drawn to methods of treating the conditions recited in claim 31 but rather to methods of treating CNS edema associated with the recited non-neoplastic conditions. As discussed above, the non-neoplastic conditions recited in the claims and disclosed at page 24 of the specification were either described as associated with edema or known to be associated with CNS edema, including cerebral edema. The specification discloses fusion receptor proteins that inhibit VEGF and methods of making said VEGF antagonists. See for example the specification at page 8, line 4 to page 9, line 2 and working example 3. The specification discloses dosage regimens and administration protocols for treating CNS edema associated with the recited non-neoplastic conditions with a hVEGF antagonist, including administering the antagonist serially or in combination with another therapeutic agent, and conventional methods for monitoring the progress of the hVEGF antagonist therapy. Applicants submit selecting an effective dosage and administration protocol is within the skill of the art and does not constitute undue experimentation.

The Office Action alleges the specification does not contemplate whether treating the edema part of the condition would be contraindicated by any other symptoms that may arise from having one of the conditions. Whether treating the edema would be contraindicated by other symptoms that may arise from having one of the conditions is not relevant to satisfying the enablement requirement. Other governmental agencies, such as the FDA, have been assigned the responsibility of ensuring the safety of therapeutic methods. See for example MPEP § 2164.05.

Nevertheless, the specification recognizes that in some instances it may be beneficial to stimulate or promote revascularization once the CNS edema has been inhibited or reduced. See, for example, the specification at page 25, lines 29-31. Moreover, in view of the high level of skill in the art and guidance provided in the specification regarding VEGF and its role in edema, one of skill in the art would be able to determine without undue experimentation when treating the edema part of the condition is contraindicated.

The Office Action alleges the working example is not commensurate in scope with the scope of injuries and conditions encompassed by the conditions recited in the claims because the

working example is narrowly concerned with a specific model of stroke that causes brain edema. Applicants do not agree.

An enabling disclosure requires a reasonable correlation to the scope of the claims. For a claimed genus, representative examples coupled with a statement applicable to the genus as a whole are ordinary sufficient to comply with the enablement requirement (MPEP § 2164.02). The disclosure of a test with every species covered by a claim is not necessary for establishing enablement under 35 U.S.C. § 112, first paragraph. *In re* Wands, 858 F.2d 731 (Fed. Cir. 1998). An exemplary showing may be sufficient to establish a reasonable correlation between the showing and the entire scope of the claims when viewed by one of skill in the art. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *In re Clemens*, 622 F.2d 1029, 1036 (CCPA 1980). A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. See MPEP § 2164.06; *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (emphasis added); see also *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01.

Applicants' disclosure demonstrates that VEGF plays a role in CNS edema formation. Example 7 demonstrates that antagonism of VEGF in a rat model of focal ischemic injury with reperfusion reduces CNS edema formation.

As discussed above, the non-neoplastic conditions are described in the specification and/or are known to be associated with CNS edema, such as cerebral edema, and the specification discloses dosage regimens and administration protocols for treating CNS edema. Therefore, it would have been reasonably expected that one of skill in the art could treat CNS edema without undue experimentation.

In view of the forgoing, Applicants submit one of skill in the art could have practice the full scope of the claims without undue experimentation. Withdrawal of the enablement rejection is respectfully requested.

Anticipation

Claims 1, 3-5, 11-13, 39, and 40 were rejected under 35 U.S.C. § 102(b) as anticipated by Ferrara. Applicants respectfully traverse this rejection.

The Office Action alleges Ferrara anticipates the claims because the active step of the claimed methods is the same as the active step of the methods taught in Ferrara. Applicants have amended the active step of claim 1 to positively set forth administering an amount of a hVEGF antagonist to reduce CNS edema. Ferrara does not disclose administering an effective amount of a hVEGF antagonist to reduce CNS edema. Ferrara therefore does not disclose all the elements of the claims.

The Office Action alleges that Ferrara teaches that hVEGF antagonists are useful in the treatment of disease or disorders characterized by undesirable vascular permeability, such as edema associated with brain tumor. The Office Action asserts this disclosure anticipates the claimed methods. Applicants respectfully do not agree.

The disclosure in an asserted anticipating reference must provide an enabling disclosure of the claimed subject matter. Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. See MPEP §2121.01 citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). A reference contains an enabling disclosure if one of ordinary skill in the art could have combined the publication's description of the invention with their knowledge to make the claimed invention. See MPEP § 2121.01 citing *In re Donohue*, 766 F.2d 531, (Fed. Cir. 1985). Applicants submit Ferrara does not enable the treatment of CNS edema with a hVEGF antagonist.

As presented in the Declaration of Dr. Van Bruggen, it was unknown if the inhibition of VEGF by an antagonist would be sufficient to inhibit cerebral edema *in vivo*. Contradictory evidence of the role of VEGF in cerebral edema existed in the literature at the time of the invention. Hayashi et al. (1998, *J. Cereb. Blood Flow Metab.*, 18:887-895) reported that VEGF itself when applied topically to the surface of a reperfused rat brain after transient cerebral artery occlusion reduced ischemic brain damage, infarct volume, and edema formation. Studies correlating peritumoral edema formation with increased levels of mRNA expression in tumor cells, while suggesting a role for VEGF in edema, presented no evidence of direct causation. In

some correlative studies, the expression of VEGF mRNA in tumor cells may have been linked to pathologies other than edema formation, such as angiogenesis or mitogenesis. See, for example, Van Bruggen Declaration at page 2 and 3.

Ferrara does not anticipate the claims because the reference does not enable the treatment of CNS edema with a hVEGF antagonist. Withdrawal of the anticipation reference is respectfully requested.

Obviousness

Claims 1, 6, 14-21, 30-38, 42, and 43 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ferrara in view of Bates and further in view of Aiello or Ozaki. Applicants respectfully traverse this rejection.

The Office Action alleges Ferrara teaches methods of treating diseases or disorders associated with edema but fails to specifically identify disorders such as the non-neoplastic condition of ischemic stroke or head injury. The Office Action asserts Bates teaches that VEGF has a direct effect on microvessels to increase vascular permeability and that Ozaki teaches that VEGF has a direct effect on retinal blood vessels to increase vascular permeability and that VEGF causes blood-retinal barrier breakdown. The Office Action asserts the teachings of Bates and Ozaki together with the teaching by Aiello that various cell types in response to hypoxia, including glial cells, produce factors such as VEGF that lead to increased vascular permeability would have directed one of ordinary skill in the art to use the hVEGF antagonists taught by Ferrara to treat edema due to a non-neoplastic condition. Applicants respectfully do not agree.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court in a recent case, a combination is obvious if it is no more than the predictable use of known elements according to their established functions and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. __ (2007). To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* A "reasonable expectation of success" is the

standard with which obviousness is determined. MPEP § 2141; *Hodosh v. Block Drug Co.*, 786 F.2d 182, 187 n.5 (Fed. Cir. 1986).

The initial burden to make a *prima facie* case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993). Applicants submit the Office Action has not established a *prima facie* case of obviousness because, in the least, the Office Action has failed to establish that one of skill in the art in view of the cited combination of references had a reasonable expectation of successfully arriving at Applicants' claims.

As discussed previously, contradictory evidence of the role of VEGF in cerebral edema existed in the literature at the time of the invention. Hayashi et al. (1998, *J. Cereb. Blood Flow Metab.*, 18:887-895) reported that VEGF itself when applied topically to the surface of a reperfused rat brain after transient cerebral artery occlusion reduced ischemic brain damage, infarct volume, and edema formation. Studies correlating peritumoral edema formation with increased levels of mRNA expression in tumor cells, while suggesting a role for VEGF in edema, presented no evidence of direct causation. In some correlative studies, the expression of VEGF mRNA in tumor cells may have been linked to pathologies other than edema formation, such as angiogenesis or mitogenesis. The contradictory evidence in the art regarding the role of VEGF in cerebral edema indicates that one of skill in the art would not have had a reasonable expectation of successfully treating CNS edema with a VEGF antagonist.

The Office Action alleges Bates teaches that VEGF has a direct role on microvessels to increase vascular permeability. However, the reference must be read as a whole. Bates is directed to a study of mesenteric blood vessels, and does not teach or suggest anything regarding the relationship of VEGF and CNS edema. When the reference is read as a whole, Bates indicates that there is a considerable amount of variation in the ability of microvessels to respond to VEGF, that microvessels have differing functional phenotypes, and that the variation in phenotypes among microvessels includes differing distribution of receptors, variation in coupling of receptors to second messenger pathways, differing responses to activation of the second messenger system, and distribution of cells of differing phenotypes along the vessel. See Bates at page H2526, second column and page H2527, first column. Bates analyzed the effects of VEGF on microvessels in the mesentery of frogs and not the central nervous system or brain. There is no indication in Bates that microvessels in frog mesentery and central nervous system

have the same functional phenotype (*e.g.*, the same distribution of receptors, the same coupling of receptors to second messenger pathways, the same response to activation of the second messenger system, or the same distribution of cells along the vessel). In view of the variation in the ability of microvessels to respond to VEGF as taught in Bates, one of skill in the art would not have been able to predict how microvessels in the central nervous system or brain would respond to VEGF absent Applicants' disclosure.

Aiello et al. discusses the use of small molecule protein kinase C inhibitors to inhibit ocular endothelial growth and capillary permeability. This reference does not teach or suggest that inhibition of VEGF by an antagonist that inhibits interaction of a hVEGF with a hVEGF receptor can or should be used in the treatment of CNS edema, stroke, or cerebral edema. In fact, the direct stimulation of protein kinase C demonstrated an increase in permeability similar to VEGF. See column 16 at lines 13-15. Thus, at least with regard to permeability, Aiello only demonstrates the effects of intracellular inhibitors of a different molecule, not intercellular antagonists of VEGF that inhibit hVEGF-hVEGF receptor interactions, as claimed in the present invention.

Moreover, the examples of Aiello et al. are directed to injecting exogenous VEGF into the eye and do not describe a more complex situation in which expression of VEGF and other factors have already been elevated. Conditions including injury, diabetes, macular degeneration are complex and several mediators are elevated. The Aiello reference does not teach or suggest that inhibition of endogenous VEGF would reduce CNS edema under those circumstances.

Similarly, the Ozaki et al. paper indicates that implantation of a pellet containing exogenous VEGF into the eye is associated with retinal neovascularization and vascular dilation. However, there is no teaching or suggestion that inhibition of endogenous VEGF would reduce CNS edema when other endogenous factors are also elevated or after an event in which expression of VEGF and other factors have already been elevated.

In support of the points in the Declaration of Dr. Van Bruggen, another post filing date reference indicates that the role of VEGF in edema formation was unclear. For example, the Quam et al, reference indicates that the definitive role of VEGF in diabetic blood-retinal breakdown was unknown by as late as 2001 (Quam et al., *Investigative Opthamology and Visual*

Science 42:2408 (2001.)). Several other factors are elevated and other cell types, such as inflammatory cells, are present when an event such as trauma, hypoxia, or ischemia occurs.

The Office Action alleges the Declaration of Dr. Van Bruggen is not persuasive in view of Bates and Ozaki. Applicants strongly do not agree.

The ultimate determination of patentability must be based on consideration of the entire record by a preponderance of the evidence with due consideration to persuasiveness of any arguments and secondary evidence. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992). Rebuttal evidence taken as a whole should be weighed against the evidence supporting the *prima facie* case of obviousness. MPEP §§ 716.01(d) citing *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984) and 2144.08(II)(B). The references described by Dr. Van Bruggen indicate that the relationship of VEGF and edema in central nervous system and brain was not clear and that in view these contradictory references it could not be predicted at the time of the invention if the inhibition of VEGF by an antagonist would inhibit CNS edema formation. Bates and Ozaki do not teach or suggest otherwise. Bates discloses there is a considerable amount of variation in the ability of microvessels to respond to VEGF. Ozaki does not teach or suggest that inhibition of VEGF would reduce CNS edema when other factors are also elevated. These references therefore do not provide any relevant evidence that rebuts the Van Bruggen Declaration.

As discussed above, a "reasonable expectation of success" must be established by a preponderance of the evidence. Absent Applicants' disclosure, one of skill in the art could not predict that a VEGF antagonist could or should be used to treat CNS edema. Applicants therefore submit the Office Action has not established a *prima facie* case of obviousness because the Office Action has failed to establish that the combination of references disclose all of the elements of the claims and failed to establish that one of skill in the art had a reasonable expectation of successfully arriving at Applicants' claims.

Withdrawal of the obviousness rejection is respectfully requested.

Interview Request

Applicants request an interview with the Examiner and her supervisor upon receipt of these papers.

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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